Original Report

Introducing a Novel Model to Estimate National and Global Measles Disease Burden

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ABSTRACT

Objectives: In discussions of expanded measles control, elimination, and possible eradication, better estimates of disease burden are increasingly important to target vaccination control measures. Because global surveillance for measles is inadequate, a model to quantify country-specific estimates of measles disease burden was formulated to help policy-makers consider control options.

Methods: Country-specific demographics, developmental status, historic vaccine coverage rates, and age-specific vaccine efficacy and attack rates were used to determine the number of measles cases and deaths for 5-year periods.

Results: The model estimates an annual global incidence of 32 million measles-susceptible persons (~25% of the global birth cohort), resulting in 28 million cases and 691 thousand deaths. Eighty-four percent (578,000) of the global deaths occur in the World Health Organization African and Southeast Asian regions. Twenty countries account for 82% of deaths attributable to measles. In nine countries, over 2% of the birth-cohort are estimated to die from measles.

Conclusions: This methodology quantifies country- and age-specific measles disease burden and establishes regional and global disease patterns, allowing aggregations by income groups and regions, which aids policy formulation. The data may be continuously updated, based on dynamic changes in vaccine coverage rates and the incorporation of national vaccination campaigns.

Key Words: *child mortality, global disease burden, measles, models, vaccines*

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Measles is both endemic and epidemic throughout the world, and therefore, it is difficult to quantify global disease burden at any one time. Although the World Health Organization (WHO) receives reports of measles disease from ministries of health through regional offices, these frequently represent an underestimation of the true incidence. As countries have variable reporting systems, there are no simple extrapolation techniques to quantify global disease burden. In discussions centered on expanded measles control, elimination, and possible eradication, better estimates of disease burden are increasingly important to focus and target vaccination control measures.[1]

Given the unreliable accuracy of reported measles cases, the WHO Expanded Programme for Immunizations (EPI) has used models to estimate disease burden. The WHO estimates the number of susceptible persons in each annual birth cohort as a function of measles vaccination rates and a differential vaccine efficacy based on age of administration. For each country, 80% of susceptible persons are assumed to develop measles. For those countries that have adopted a campaign approach using pulse vaccination for measles control,[2] 1% of susceptible persons are assumed to develop measles (Olive JM. World Health Organization. Personal communication). Country-specific case fatality rates, ranging from 0.05% to 6% (EPI. Unpublished data) are then applied to the number of cases determined for each country, to estimate the number of measles-related fatalities. The WHO model has the advantage of simplicity and routine historic use.

However, with the introduction of mass campaigns of vaccination against measles and the sustained high coverage rates in many countries, the current EPI model does not adequately address many of the subtleties of measles transmission dynamics, such as age-specific attack rates and population immunity, that offer an extended herd effect at the local, national, regional, and global level.[3] With expanded efforts of measles control, reliable estimates of disease burden become increasingly important, to help guide policy planning and vaccine strategies. In this article a new methodology to quantify global measles disease burden is described that accounts for the age-distribution of measles susceptible persons, morbidity, and mortality, providing a framework for measles control

efforts and economic assessments of various vaccination strategies.

METHODS

An epidemiologic model incorporating stochastic features, such as outbreak events, and compartmentalized by age-group and geographic features was formulated. The model incorporates country-specific population demographics, socioeconomic development status, historic coverage rates of measles vaccine (delivered routinely or through periodic campaigns), age-specific vaccine efficacy, and forces of infection (Tables 1 and 2). It also includes a stochastic factor to indicate the likelihood of virus to enter a highly vaccinated population in a specific geographic area (e.g., island population or highly vaccinated regions, such as in select populations primarily in the Americas and Europe).

Demographics

For each country, age cohorts of children 0 to 6 months, 7 to 12 months, 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years of age are derived from United Nations-published country-specific birth rates adjusted by rates of infant mortality and under 5 mortality.[4,5]

Susceptibility

Individuals in each successive birth-cohort are considered immune for the first 6 months of life, based on maternal antibodies, after which they become susceptible (Figure 1). Individuals remain susceptible until they are successfully immunized or they develop disease, after which they remain immune for life. The number of susceptible persons in each age cohort is dependent on historic vaccination coverage rates (including campaigns),[6] age-specific vaccine efficacy, and immunity from natural disease as estimated by previous iterations of the model (see Appendix A for formulae).

Table 2. Age-Specific Attack Rates of Susceptible Persons (Forces of Infection)* during Outbreak Periods

Age	*Low Income (%)*	*High Income (%)*
6–12 mo	0.121	0.121
1–4 y	0.333	0.121
5–9 y	0.345	0.345
10–14 y	0.201	0.201
15–19 y	0.144	0.144
20–75 y	0.068	0.068

*Adapted from Anderson RM, May RM.[8]

Disease Incidence

The measles basic reproductive rate (R_0) indirectly determines the threshold level of population immunity at which pathogen transmission continues to occur.[7] When the proportion of the susceptible population exceeds the critical threshold of $1/R_0$ (approximately 6.7% for measles), the model predicts the occurrence of ongoing transmission.

Country-specific outbreaks and endemic disease are assumed to occur whenever the critical susceptible

Table 1. General Model Assumptions

Parameter		*Data Source*
Population structure cohorts		
Country-specific		United Nations Population Division,[4] UNICEF[5]
Surviving birth cohort		Surviving infants estimated using birth-rates adjusted for rates of infant mortality and <5 mortality
1–4 years		
5–9 years		
10–14		
15–20		
Vaccination coverage		
Country-specific		Expanded Program on Immunization[6]
Vaccine immunogenicity		
85% for vaccination at <12 months		Orenstein et al[15]
95% for vaccination at >12 months		
Force of infection		
See Table 2		Anderson and May,[8] Grenfell and Anderson,[9] Nokes and Anderson[10,11]
Stochastic factor*		
Nonisland countries	0.00070	Reported incidence of estimated 1- to 14-year-old susceptible persons from selected countries,†
Island countries	0.00008	following either campaigns or routine high coverage rates in excess of 95%
Case:fatality rates		
Country-specific		EPI. Unpublished data

*Applied to those countries that effectively have continuously reduced population immunity in the 1- to 14-year-old age group of less than 1/R0 (<6.7%) either through routine coverage or with the implementation of campaign(s).
†Countries include Argentina, Belize, Bolivia, Canada, Chile, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Uruguay, United States, Venezuela; Island countries include The Bahamas, Barbados, Cuba, Dominica, Grenada, Guyana, Haiti, Jamaica, Puerto Rico, Trinidad & Tobago.

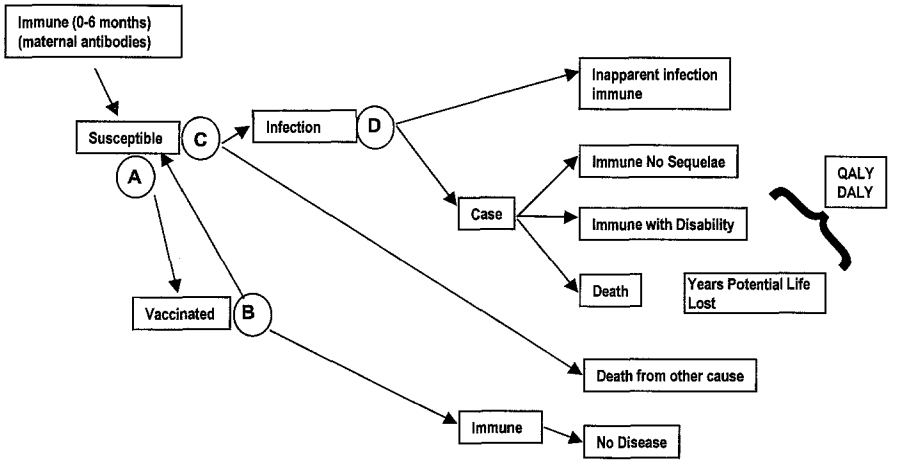

Figure 1. Abbreviated schematic of deterministic model of measles transmission incorporating a vaccine-preventable strategy. Assuming all persons are susceptible to measles infection 6 to 9 months after birth (postmaternal antibody protection), there are variable probabilities (letters A–D) for passage into other transitional states throughout the lifetime of an individual. The variable probabilities are stratified geographically and by age and incorporate overall population immunity. For each country, birth cohorts from the past 20 years are successively followed to account for the impact of national vaccination programs on current disease burden. A, vaccination coverage rate (age-specific and by dose); B, vaccine efficacy by dose and timing of administration; C, age specific attack rate (varies by population density of susceptible persons); D, probabilities of progression to each outcome state.

population exceeds 6.7%. Historically, during these outbreak periods, an age-specific force of infection or attack rate in the susceptible population was applied leading to country-specific number of cases, deaths, and new immune persons to enter the next age cohort. In classic deterministic models, forces of infection are derived by numerous population-specific parameters, including average age of infection and the lifetime probability of disease in the absence of vaccination.[7] Attack rates of susceptible persons—forces of infection (see Table 2), for each country and age group were assumed on the basis of demographic structure and the historic control with vaccination as documented in previous studies.[8-11] Two sets of values were used, one for countries with a historic early-age onset of measles attributable to age structures predominately composed of children less than 15 years of age (most developing countries); the second for countries that traditionally have had a later onset of measles.

For countries with estimated immunity in the 1- to 14-year-old age group of less than $1/R_0$ (6.7%), measles outbreaks were assumed not to occur. However, in the absence of global eradication, measles cases could occur due to nonsustained transmission from imported cases. To account for these cases, stochastic factors were applied to simulate the chance infection of a susceptible person from imported virus. The stochastic factor was derived from the average reported number of cases as a percentage of the calculated susceptible population 1 to 14 years of age from countries in the Americas that met the criteria of estimated population immunity of less than $1/R_0$. Because of the relative isolation of island nations, two stochastic factors were derived, one for island, and another for nonisland populations. For countries where outbreaks would not normally occur (population susceptibility <6.7%), the annual number of cases was estimated by multiplying the appropriate stochastic factor by the estimated susceptible population.

RESULTS

A susceptibility profile for each country was determined by the annual accumulation of measles susceptible persons aged 1 to 20 years (see Figure 1). Although the model estimates the percentage accumulation of susceptible persons for each country, it does not predict the precise year when outbreaks will occur. However, in the absence of further control measures, it does estimate the number of cases and deaths that would occur on average over every 5-year period (assuming the maintenance of current levels of susceptible-person accumulation through vaccination and natural disease). These estimates are annualized by dividing by 5 and are aggregated by region (Figures 2 and 3) (Table 3).

The model estimates a global annual incidence of 32 million persons susceptible to measles, 67% in the WHO designated African (AFR) and Southeast Asia regions (SEAR), populations which account for 45% of the global infant cohort. Approximately 25% of each successive 0- to 4-year-old global cohort remain susceptible to measles each year, owing to low vaccination rates and vaccine failures. By region, the accumulation of measles susceptible persons is most pronounced in AFR (54%), followed by the Eastern Mediterranean (31%) and SEAR (26%). This contrasts to the American region where only 5% of each successive 0- to 4-year-old cohort remains susceptible to measles, with the assumed current maintenance of periodic campaigns.

Owing to the annual accumulation of susceptible persons, on average, an estimated 28 million cases of measles is expected each year. The global case distribution is similar to that of the distribution of susceptible persons. Over 16 million (58%) cases are estimated to occur in SEAR and AFR regions. Given the higher case fatality rates for countries in these regions, 578 (84%) of the 691,000 estimated global measles deaths would occur in these two regions.

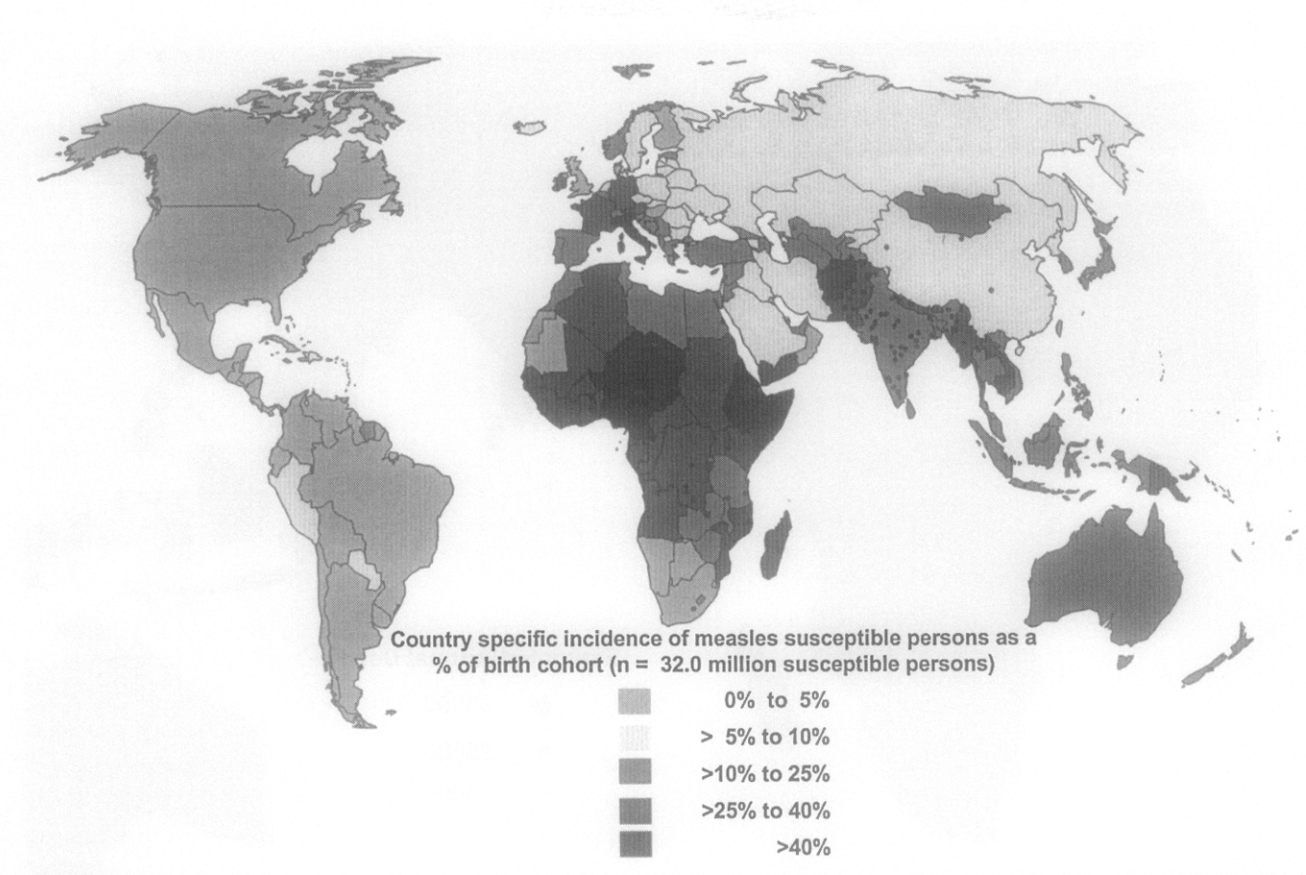

Figure 2. Distribution of the annual incidence of measles-susceptible persons (shown as a percentage of the national birth cohort) and distribution of cases by country (n = 27.6 million cases; 1 dot = 200,000).

The 20 countries that contribute the most to measles mortality are listed in Table 4. These countries comprise 59% of the global surviving birth cohort but account for 82% of the average annual deaths due to measles. Although, most deaths are estimated to occur in India, the highest incidence occurs in Niger, Afghanistan, and Somalia. The model estimates that, in nine countries, over 2% of the birth cohort die from measles. A comparison of mortality rates in children under 5 years of age and rates of death attributable to measles for each country is included (see Table 4). Assuming that most deaths due to measles occur in children less than 5 years old, between 5% and 10% of mortality in children under 5 years of age is attributable to measles in almost all of these countries.

DISCUSSION

Concern has been raised regarding the formulation of public health policy in the absence of adequate data.[12] Although global estimations of measles exist in the Global Burden of Disease study published in 1996,[13] to date, the cited source of the methodology used to derive the estimates has yet to be published. Given the limitations of countries to adequately conduct surveillance for measles, this model allows one to quantify current disease burden attributable to measles and the expected impact of new control measures. Because this method characterizes the susceptible population by age groups, it also allows for specific estimates of cases and deaths that occur at different ages, thereby allowing for a quantification of the years of potential life lost and the disability-adjusted life years (DALY).[14] These metrics allow one to integrate age-specific morbidity and mortality for comparisons to other diseases. Although age-specific case-fatality rates were not included, one might further elaborate this model as additional data become available.

This model represents the next step of refinement in the setting of limited data to better quantify global disease patterns. Further refinements may be possible, such as that which may be afforded by serosurveys of different countries to refine country- or region-specific forces of infection, to account for regional herd effects. However, the time and expense of such data collection must be weighed against the marginal advantages it would bring to current estimates. In addition, as better subnational data become available, the model can be modified to account for rural and urban population distributions, to more adequately reflect population-density transmission factors. However, until such data are available, this model can serve to estimate patterns of disease.

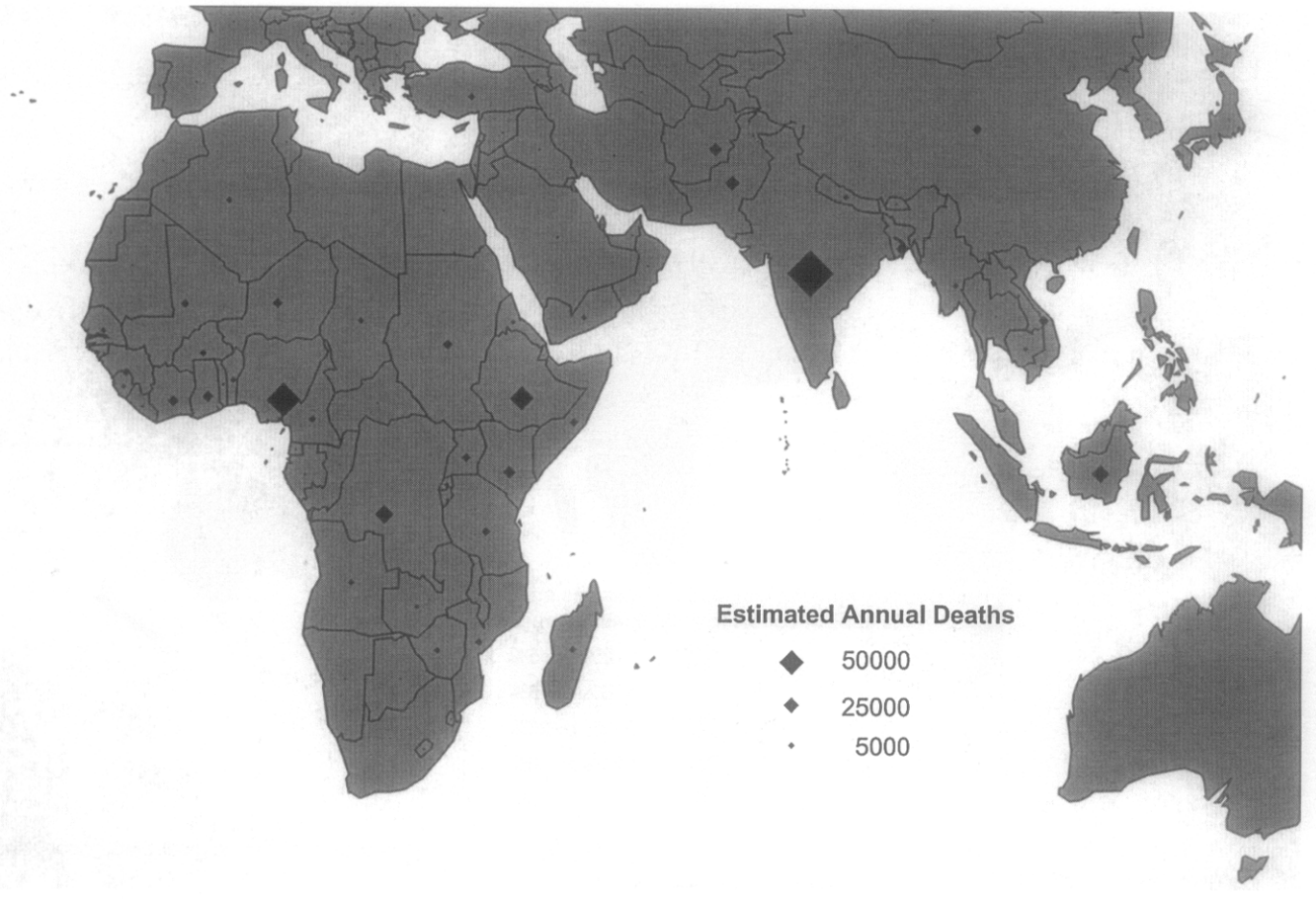

Figure 3. Distribution of estimated incidence of deaths attributable to measles by country.

As new strategies for measles control are adopted, this model can serve to estimate the expected impact. By disaggregating each country by age-specific cohorts, it allows one to assess the impact of various targeting strategies over the course of time. As more regions increase their population immunity, stochastic factors play a more important role in disease transmission. Measles disease may then be predicted more by the chance presence of measles virus importation, determined by national or regional and global levels of immunity. As immunity throughout the world increases, these contact rates of virus and susceptible persons decrease. The stochastic factors become the prime determinant of ongoing measles transmission over larger geographic areas.

LIMITATIONS

The model is limited mainly by the quality of the data that formulate it. Although, it offers a refinement over models based on global averages through its aggregation of country-specific data, the data on which the assumptions are based may be flawed. Through the appropriate use of

Table 3. Results: Population, Susceptible Persons, Susceptibility Profiles, Annual Range of Cases, and Deaths by WHO Regions

WHO Region	*Surviving Infants 129 Million (100%)*	*Estimated New Measles-Susceptible Persons Each Year* 32 Million (100%)*	*Measles-Susceptible Persons as Percentage of Surviving Infants in Region (25%)*	*Estimated Annual Cases to Occur 1997–2001* (27.6 Million)*	*Estimated Annual Number of Deaths to Occur 1997–2001* (691.0 Thousand)*
Africa	22 (17)	12 (37)	54	7.3	351.3
Americas	16 (12)	1 (2)	5	0.0	0.1
Eastern Mediterranean	15 (12)	5 (14)	31	3.8	73.5
Europe	11 (9)	2 (6)	18	2.2	8.6
Southeast Asia	36 (28)	9 (30)	26	8.8	226.4
Western Pacific	28 (22)	3 (11)	12	5.5	31.2

*Assumes maintenance of current control measures.

Table 4. Top 20 Countries Accounting for the Most Deaths Due to Measles

Country	Surviving Infants (Millions)	Estimated Incidence of Deaths Due to Measles (Thousands)	Under 5 Mortality Rate* (per 1000)	Measles Death Incidence (per 1000 <5-Year-Old Children)
India	24.0	167	111	7
Nigeria	4.4	96	191	22
Ethiopia	2.2	50	177	23
D.P.R. Congo	1.8	33	207	18
Indonesia	4.4	29	71	7
Pakistan	4.9	26	136	5
Bangladesh	3.7	21	112	6
Afghanistan	0.8	20	257	26
Kenya	1.1	16	90	15
Ivory Coast	0.6	13	150	21
Ghana	0.6	13	110	20
China	20.6	11	47	1
Niger	0.4	11	320	27
Vietnam	2.1	10	44	5
Sudan	1.0	10	116	10
Somalia	0.4	10	211	24
Uganda	0.9	10	141	11
Mali	0.4	9	220	21
Tanzania	1.1	9	144	8
Burkina Faso	0.4	8	158	19
Total	75.8	569	—	8

*UNICEF.[5]

sensitivity analysis (adjusting assumptions through their range of uncertainty) this model can offer a range of values for the outputs.

The model provides disease burden estimates over 5-year periods and cannot precisely predict when outbreaks would occur. However, through the estimates of population levels of immunity, it indicates the likelihood of an outbreak to occur, when the percentage of susceptible individuals in the population exceeds the epidemic threshold of $1/R_0$, approximately 6.7%. As such, it offers an accounting of how much disease can be predicted over the course of several years but does not attempt to account for year-to-year variations.

Deterministic models have several limitations. Although different sets of age-specific forces of infection were used based on historic patterns of transmission, they had been originally derived from "virgin" populations, unexposed to measles. They also are based on a random mixing of cases and susceptible persons resulting from a random distribution of coverage. This model only covers the age up through 20 years and does not account for rural and urban differences in transmission dynamics. The model has been formulated to allow additional data input to account for these factors as data become more readily available, such as differential coverage rates for urban and rural populations.

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Appendix A. Formulae for Estimations

The model defines the number of susceptible persons in each country for any given year by the sum of the susceptible persons in each of the five age cohorts (Sus_i) divided by the number of years (Y_i) in that cohort:

$$Sus_t = \sum_{i=0}^{5} \sum_{k=1}^{y} Pop_{ik} - (Cov_i Pop_{ik} eff_i + Sus_{(ik-1)} A_{(i-1)})/Y_i$$

Where:
Sus_t = country-specific measles-susceptible population.
Cov = reported vaccination coverage rate in age cohort.
Pop = population of cohort.
eff = age-specific vaccine efficacy.
A = force of infection per period.
Y = number of years in $cohort_i$.
For each country and age cohort, the number of cases and deaths are defined by:

$$Cases_x = \sum_{i=0}^{6} \sum_{k=1}^{y} Sus_{ik} A_i Z/Y_i$$

$$Deaths_x = Cases_t CFR_x$$

Where:
Z = Stochastic factor (1 for countries where the percentage of susceptible persons 1-14 years of age within the population exceeds $1/R_0$ or 6.7%; for all other countries, 0.0007 and 0.00008 for nonisland and island countries, respectively).
CFR_x = country-specific case fatality rates.

$$Sus_{tot} = \sum_{x=1}^{180} Sus_x$$

$$Cases_{tot} = \sum_{x=1}^{180} Cases_x$$

$$Deaths_{tot} = \sum_{x=1}^{180} Deaths_x$$

Global or regional aggregate data are determined by summing national totals of susceptible persons, cases, or deaths where x represents each national estimate of the 180 countries for which sufficient data exist.